II. REMARKS

Upon entry of the amendment, claims 1 to 10 and 50 to 57 will be pending. A marked-up copy showing the amendments to the specification and the claims is attached hereto as Exhibit A.

The subject application discloses for the first time that serpentine cell surface receptors define a specific cell lineage and provide the highest level of specificity that allows the formation of complex tissues and organs such as brain. Prior to the present disclosure, the "address molecules" that define cell lineage were not known. By analogy to a telephone number, which includes an area code, a prefix, and a unique four digit identifier number, the subject application discloses that serpentine receptors provide the unique "four digit" identifier that specifies cell lineage.

A. Regarding the Amendments

The specification has been amended has been amended to correct typographical errors, wherein exponents, which should be shown as superscripts, inadvertently were shown as subscripts, and to substitute a "hyperlink" with text referring to the specified website. As such, the amendments merely correct typographical errors or address a formality, and do not add new matter. Accordingly, it is respectfully requested that the amendments to the specification be entered.

Pursuant to the restriction requirement, claims 11 to 49 are cancelled herein without disclaimer, and without prejudice to Applicant's pursuing prosecution of subject matter encompassed within one or more of the claims in an application claiming the benefit of priority of the subject application.

Claim 1 has been amended to clarify that the serpentine marker is a cell surface "receptor" and to indicate that the recited binding agent binds to cells "expressing the receptor." The amendments are supported, for example, at page 3, lines 11-15; and page 8, lines 16-17. Claim 1 also has been amended to more clearly indicate that the serpentine cell surface receptor

is "indicative of a specific cell type or lineage." The amendment is supported, for example, at page 3, lines 1-5. As such, the amendments to claim 1 do not add new matter.

Claim 2 has been clarified that the method further comprising separating "from" the cells obtained according to a method of claim 1, "a cell or cells expressing" at least one additional marker. The amendment is supported, for example, at page 9, line 24, to page 10, line 4, and, therefore, does not add new matter.

Claim 5 has been amended to clarify that the term "derivative" refers to a derivative of an antibody as recited. The amendment is supported, for example at pages 11 to 14 of the specification, which describe numerous antibody derivatives, including, for example, humanized antibodies, antibody fragments derived from combinatorial libraries, antibody fragments such as Fab' and Fv fragments, and CDR peptides, and, therefore, does not add new matter.

Claim 7 has been amended to clarify that the step of "analyzing the DNA" is "to detect a sequence indicative of lineage" of the specific cell type. The amendment is supported, for example, at page 28, lines 2-5, and, therefore, does not add new matter.

Claim 9 has been amended to correct a typographical error, wherein the term "blot" inadvertently was capitalized. As such, the amendment merely corrects a typographical error, and does not add new matter.

New claims 50 to 57 have been added. New claim 50 is based on claims 1 and 2 as originally filed, and, in part, on claim 1 as amended as described above. As such, new claim 50 is supported by the specification and the claims as originally filed and, therefore, does not add new matter. New claims 51 to 57 are supported by claims 3, 4 and 6 to 10, respectively, as originally filed, and, therefore, do not add new matter.

B. Objection to the Specification

The specification is objected to as containing an embedded hyperlink. The specification has been amended to attend to this matter and, therefore, it is requested that the objection be withdrawn.

C. Rejections under 35 U.S.C. § 112

The rejections of the claims under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite are respectfully traversed.

It is stated in the Office Action that the term "substantially enriched" is a relative term which renders the claim indefinite. However, there is no requirement that a level or amount of enrichment be specified and, it is submitted, any amount of enrichment from the state in which the specific cell type naturally occurs is sufficient to meet the limitation. Furthermore, one skilled in the art reading the claims in view of the specification would know that a method of the invention, which separates a specific cell type based on its binding to an agent that "binds specifically" to cells expressing a serpentine receptor, results in a composition that is substantially enriched in the specific cell type. As such, it is submitted that the term "substantially enriched" as recited in the claims and in view of the specification is clear and definite and, therefore, requested that this ground of rejection be removed.

It is also stated in the Office Action that the term "binding agent" is not defined and, therefore, the metes and bounds cannot be determined. However, the claims require that a "binding agent binds specifically" to a cell or cells expressing a serpentine cell surface receptor, and the specification provides examples of such binding agents, including, for example, an antibody or a ligand specific for the serpentine receptor (see, for example, page 3, lines 1-5). As such, it is submitted that the term "binding agent" as recited in the claims and in view of the specification is clear and definite and, therefore, requested that this ground of rejection be removed.

It is further stated in the Office Action that the term "serpentine cell surface marker" is unclear, and that the metes and bounds of the term cannot be determined. As an initial matter, the term has been amended to recite "serpentine cell surface receptor." In this respect, it is pointed out that the specification discloses that serpentine cell surface receptors include those receptors characterized by seven helical transmembrane domains (see page 8, lines 1-4). Furthermore, Applicant points out that the term "serpentine cell surface receptors" is routinely used and well known in the art (see, for example, Smith et al., Prog. Biophys. Mol. Biol. 71:313-341, 1999, pages 313-316 of which are attached hereto as Exhibit B; see page 315, referring to a 1997 publication; the Examiner also is invited to search, for example, at www.google.com using the terms "serpentine family" and "receptor"). Thus, in view of the amendment and of knowledge in the art, it is requested that this ground of rejection be removed.

In addition, it is stated in the Office Action that the terms "associated with" and "selecting for" render claims 2 and 3 unclear. The terms objected to have been deleted from the claims and, therefore, it is submitted that these rejections are moot.

It is also stated in the Office Action that the term "or derivative thereof" in claim 5 is unclear. It is stated, for example, that it is not clear if the term refers to antibodies, ligands, or agents in general. Claim 5 has been amended to clarify that the term "derivative" refers to a derivative of an antibody. The specification exemplifies numerous derivatives of an antibody, including, for example, humanized antibodies, antibody fragments derived from combinatorial libraries, antibody fragments such as Fab' and Fv fragments, and CDR peptides (pages 11 to 14). As such, in view of the amendment and of the disclosure, it is requested that this rejection be removed.

It is further stated in the Office Action that the term "analyzing the DNA" in claims 7 to 9 is not clear as to the type or nature of the analysis. Claim 7 has been amended to clarify that the DNA is analyzed "to detect a sequence indicative of lineage" of the cells. The specification discloses numerous methods for performing such an analysis, including amplification methods

(page 18, line 12, to page 19, line 9), and hybridization methods (page 19, line 10, to page 20, line 2 (see, also, page 20, line 3, to page 21, line 18; and page 28, lines 2-20). As such, it is submitted that one skilled in the art reading amended claim 7 in view of the specification clearly would know the metes and bounds of the claimed subject matter.

It is further alleged with respect to claims 7 to 9 that the claims "omit essential steps". It is stated that the method steps should include at least a contacting step...a detection step...and a correlation step." (Office Action at page 4, paragraph 12). Claim 7 has been amended to more clearly indicate that the method requires "analyzing the DNA of the cells to detect a sequence indicative of lineage." It is submitted that amended claim 7 clearly apprises one skilled in the art as to the scope of the invention and how to practice the claimed methods.

It is further submitted that recitation of additional steps, for example, recitation of a "contacting step" or a "correlating step" would unnecessarily limit the subject matter to which Applicant is entitled because a separate "contacting step" or a "correlating step" may not be necessary to perform the required "analyzing". For example, the specification discloses that the step of analyzing the DNA can be performed in various ways, including by an oligonucleotide ligation assay or an RNAse protection assay (page 18, lines 13-20), or by detecting a genetic fingerprint using a microarray analysis (page 20, lines 2-16), or using physical mapping methods such as positional cloning (page 28, line 21, to page 22, line 5), and additional methods of analyzing DNA are well known and routine in the art. Thus, depending on the method of analyzing the DNA, it may not be necessary to perform a separate "contacting step" to practice the method and, even if such a step is necessary, any of a number of different reagents can be contacted with the DNA, again depending on the particular method being practiced. As such, it is submitted that recitation of a separate contacting step would unnecessarily limit the claims.

Similarly, with respect to a "correlating step", it is submitted that any of various correlations can be made, including, for example, by directly determining the sequence and recognizing it as characteristic of a lineage, or by comparing migration of a band in a gel from a

specific cell type obtained according to a method of the invention with that of a known cell type or with a standardized tabulation of migrations for DNA known to be present in cells of a defined lineage, or by any other method specific to the analysis being performed. As such, it is submitted that the recitation of a correlating step would unnecessarily limit the subject matter to which Applicant is entitled because a "correlating step" may not be necessary "to detect a sequence indicative of lineage" and because, even if such a step is necessary, the skilled artisan will know that a sequence indicative of a lineage can be identified using any of various methods.

In summary, it is submitted that claim 7 clearly apprises one skilled in the art of the scope of the invention and how to practice a method of the invention, and that the recitation of additional steps would unnecessarily limit the scope of the invention to which Applicant is entitled. As such, it is requested that this ground of rejection be removed.

In view of the amendments to the claims and the above remarks, and further in view of the specification and of knowledge in the art, it is submitted that the claims clearly define the subject matter regarded as the invention such that one skilled in the art would know the metes and bounds of the claimed subject matter. Accordingly, it is respectfully requested that the rejections of the claims under 35 U.S.C. § 112, second paragraph, be removed.

The objection to the specification and corresponding rejection of the claims 1 to 10 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement are respectfully traversed.

It is acknowledged in the Office Action that the specification is enabling for sorting serpentine receptor positive cells from serpentine receptor negative cells. It is alleged, however, that the specification does not reasonably enable sorting any cell lineage by detecting a serpentine receptor.

The present invention is based, in part, on the discovery that serpentine receptors provide the highest level of specificity indicative of a specific cell type or lineage. The claims are directed to a method for obtaining a "composition substantially enriched in a specific cell type"

by separating cells that are bound by a binding agent specific for a serpentine receptor, which is indicative of a specific cell type or lineage, from a sample containing such cells. In view of the disclosure that serpentine receptors are indicative of a specific cell type or lineage, one skilled in the art would have recognized that a "specific cell type", i.e., cells expressing a particular serpentine receptor, could be obtained using routine methods as disclosed in the specification (see, also, obviousness rejections made in present Office Action) to obtain a composition substantially enriched in the specific cell type, as claimed.

In addition, the specification discloses that a serpentine receptor provides one of the signals involved in cell lineage. According to the "Area Code Hypothesis", the particular serpentine receptor expressed by a specific cell type relates to the last four digits of a telephone number, and additional markers such as cell adhesion molecules relate to the prefix, area code, country code, and the like of a telephone number (see, for example, page 7, lines 11-20; page 39, line 15, to page 40, line 2). Thus, the present invention provides a method to obtain a composition substantially enriched in a specific cell type, which expresses a particular serpentine receptor indicative of the specific cell type or lineage. In certain embodiments (see claims 2 and 50), the specific cell type is further characterized in that it expresses at least one additional marker (for example, a serpentine receptor and an O-CAM).

The skilled artisan also would have known that a specific cell type, which expresses a specific serpentine receptor, also can be obtained by first isolating a population of cells enriched in stem cells or other progenitor cells, and, according to a method of the invention, contacting such an enriched population of cells with a binding agent specific for a serpentine receptor and separating the cells that bind thereto, thereby obtaining a composition substantially enriched in a specific cell type. For example, it is well known that neuronal stems cells and other more mature progenitor cells can be used in transplantation studies, but that the use of such cells is limited by the diversity of cell types into which they can differentiate (see, for example, Keirstead, J. Neurosci. Res. 63:233-236, 2001, which is attached hereto as Exhibit C; see page 234, first and

second full paragraphs in left column). In view of the present disclosure, the skilled artisan would have known that a population of stem cells such as neuronal stem cells can be further selected, according to a method of the invention, by contacting the cells with a binding agent specific for a serpentine receptor, and separating cells bound by the agent, thereby obtaining a composition substantially enriched in a specific cell type or lineage. Such specific cell types then can be used for transplantation experiments and have the advantage that cells destined to differentiate along a specific cell lineage can be used for the procedure.

It is stated in the Office Action that the claims broadly encompass isolating any specific cell type that expresses a serpentine receptor. It is also stated that the specification prophetically teaches that serpentine receptors are cell lineage markers, and is alleged that such teachings are supported by very limited guidance as to the similarities between EST's and variant cell lineages, and there is no evidence that such markers are indicative of a particular lineage (Office Action at paragraph bridging pages 5-6). However, the specification discloses, for example, 1) that olfactory neurons that are widely dispersed, but contain the same olfactory serpentine receptor, target their processes to specific pairs of bilaterally symmetrical glomeruli in the olfactory bulb (see page 35, lines 14-22), and 2) that olfactory serpentine receptors are expressed on diverse cell types, including cells types that are not involved in olfaction (see Table 1, page 48). Based, in part, on the expression of olfactory serpentine receptors on a wide variety of cell types other than neural cells involved in olfaction, and on the correlation of specific serpentine receptor expression with targeting of olfactory neurons to specific positions within the olfactory bulb in the brain, it is disclosed in the specification that olfactory serpentine receptors have a role separate from olfaction and, more specifically, that they are involved in determining positioning, and, therefore, indicative of lineage of specific cell types. As such, and absent objective evidence to the contrary, it is submitted that one skilled in the art, viewing the subject application, would have known that serpentine cell surface receptors can be indicative of cell lineage and would

have known that a composition enriched substantially in a specific cell type can be obtained using the claimed methods.

It is further alleged that the data necessary for practicing the invention is improperly incorporated by reference. Applicant is uncertain as to which data the Examiner refers. It is noted that there was an objection to reference in the specification to the NCBI website, which was in the form of a hyperlink. However, the database was not "incorporated by reference" and, indeed, is not necessary to practice the invention. As disclosed in the specification, the database search was used to determine whether olfactory serpentine receptors had been reported to be expressed in tissues other than those associated with olfaction (page 35, line 22, to page 36, line 20). As shown in Table 1 (page 48), the olfactory serpentine receptors were found to widely expressed in various tissues, thus supporting Applicant's position that such serpentine receptors, in addition to having a role in olfaction, can have an additional function in determining cell lineage (see, for example, page 37, lines 9-11). Accordingly, it is respectfully requested this rejection be removed, or that the basis for this rejection be clarified.

In summary, it submitted that, in view of the specification, one skilled in the art would have known that expression of serpentine cell surface receptors is indicative of cell lineage, and, using routine methods as disclosed in the specification or otherwise known in the art, would have known how to obtain a composition substantially enriched in a specific cell type as claimed. Accordingly, it is respectfully requested that the objection to the specification be withdrawn and that the corresponding rejections of the claims as lacking enablement be removed.

D. Prior Art Rejections

The rejection of claims 1, 2 and 4 to 7 under 35 U.S.C. 103(a) as allegedly obvious over Nef and Nef, or Drutel et al., or Vanderhaeghen et al, or Mombaerts et al, in view of Janeway and Travers, or Stites et al., or Schlossman et al., or Seed et al., or Wysocki et al., or Aruffo et al., or Heller et al., [or Cruikshank] is respectfully traversed.

It is stated in the Office Action that Nef and Nef describe olfactory marker positive cells, methods of identifying such cells, and that such cells have olfactory and neurologic function, and further describe analyzing the DNA in such cells; that Drutel et al. similarly describe olfactory marker positive cells, including a function of such cells in olfactory development, sperm chemotaxis, and odor and taste recognition; that Vanderhaeghen et al. similarly describe olfactory marker positive cells, including an olfactory function of such cells; and that Mombaerts et al. similarly describe olfactory marker positive cells, including neurologic and olfactory functions of such cells, but that the above references do not describe sorting or enrichment of cells expressing such olfactory markers. The secondary references are provided as variously describing methods of such sorting or enrichment of cells. As such, it is alleged that one of ordinary skill in the art would have been motivated to use the methods of the secondary references to enrich for cells expressing an olfactory receptor as described in the primary references in order to test for olfactory, sperm chemotaxis, or neurologic function.

Applicant submits, however, that one of ordinary skill in the art would not have been motivated to combine Nef and Nef, or Drutel et al., or Vanderhaeghen et al., or Mombaerts et al. with the secondary references because there is nothing in any of the primary references that would motivate one to separate such cells from a sample. It is stated in the Office Action that the motivation to combine the references would be to enrich for cells expressing an olfactory receptor in order to test for olfactory, sperm chemotaxis, or neurologic function. However, there is nothing in any of the references to suggest such testing. For example, there is no indication as to what type of olfactory or neurologic function could be tested using such cells. Furthermore, while mention is made that olfactory receptors may be involved in sperm chemotaxis, such mention merely is with respect to "suggested" role for the receptor (Drutel et al., page 33, paragraph bridging columns; citing to Parmentier et al., 1992, and Vanderhaeghen et al., 1993, neither of which was provided in support of the rejection).

It is well recognized that the motivation or suggestion for combining references must be derived from the references, from knowledge in the art, or from the nature of the problem to be solved (see Sibia v. Cadus, 55 USPQ2d 1927 (Fed Cir 1997)). In the present case, there is nothing but a general statement of potential tests that can be performed using an enriched population of cells, with no suggestion as to how such tests would be performed. As such, it is submitted that, absent Applicant's disclosure, one skilled in the art would not have been motivated to combine the cited references because there is nothing specific in the references or in the art that would provide the necessary motivation, and, therefore, requested that the rejection be removed for this reason as well.

Applicants point out that new claims 50 to 57 require separating from a sample cells that express a serpentine cell surface receptor, and further separating from the cells expressing the receptor a cell or cells that express at least one additional marker. It is submitted with respect to the new claims that, even if one of ordinary skill would have been motivated to combine the cited references to separate cells expressing a serpentine receptor from a sample, none of the references, either alone or in combination, teaches or suggests further separating from the cells expressing the receptor, a cell or cells that express at least one additional markers. As such, it is submitted that the claimed invention would not have been obvious in view of the cited references and, therefore, respectfully requested that this ground of rejection be removed.

In summary, it is submitted that one of ordinary skill in the art would not have been motivated to combine the cited references because there is nothing in the references themselves, or in the art in general, that would have led the artisan to combine the references. However, even if for argument sake, it is considered that one in the art would have combined the references, there is nothing in the references, either alone or in combination, that would have led the artisan to further separate from a population of cells expressing a serpentine receptor a cell or cells further expressing an additional marker such as a cell adhesion molecule because, prior to Applicant's disclosure, it was not known that serpentine cell surface receptors constitute the

ultimate "address molecules" that define cell lineage and provide the high level of specificity required for the formation of complex tissues and organs such as the brain. As such, it is submitted that the claimed invention would not have been obvious in view of the cited references, either alone or in any combination. and, therefore, respectfully requested that the rejection of the claims under 35 U.S.C. 103(a) be removed.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: December 31, 2001

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Enclosure: Exhibits A, B and C

EXHIBIT A

MARKED-UP COPY SHOWING AMENDMENTS

TO SPECIFICATION AND CLAIM

A. In the Specification

The amendment at pages 20 to 21 are as follows:

--The biological chip plates used in the methods of this invention include biological chips. The array of probe sequences can be fabricated on the biological h103chip according to the pioneering techniques disclosed in U.S. Pat. No. 5,143,854, PCT WO 92/10092, PCT WO 90/15070, or U.S. application Ser. Nos. 08/249,188, 07/624,120, and 08/082,937. The combination of photolithographic and fabrication techniques may, for example, enable each probe sequence ("feature") to occupy a very small area ("site" or "location") on the support. In some embodiments, this feature site may be as small as a few microns or even a single molecule. For example, a probe array of 0.25 mm^2 [mm.sup.2] (about the size that would fit in a well of a typical 96-well microtiter plate) could have at least 10, 100, 1000, 10^4, 10^5 or 10^6 [10_4, 10_5 or 10_6] features. In an alternative embodiment, such synthesis is performed according to the mechanical techniques disclosed in U.S. Pat. No. 5,384,261, incorporated herein by reference. Sensitive analysis of serpentine receptor nucleic acid can also be performed as described by Clinical Microsystems, using AC to detect minute changes in electron flow in dsDNA after DNA fragments hybridize to an array of DNA on a chip.--

The amendment at page 34, lines 7-22, is as follows:

Internet Grateful Med and SciSearch (ISI) databases were used for retrieval of bibliographic information. Large numbers of references including abstracts were downloaded into Procite 4 (ISI) for further searching and analysis locally as well as for formatting references. The online resources available through The National Center for Biotechnology Information, which can be accessed on the world wide web at the URL "ncbi.nlm.nih.gov", [(http://www.ncbi.nlm.nih.gov)] were used extensively in this work. The information that is reported in Table 1 was obtained by searching the dbEST database using the text string: olfactory AND receptor and the names of the tissues indicated in Table 1. The retrieved and curated information included in Table 1 represents only a partial list. The quality of the sequence data varied widely as is normal for the expressed sequence tags. Nevertheless, it was clear that this approach provided a great deal of useful information on the expression of serpentine receptor genes in a large number of different tissues. Only the retrieved sequences that are related to known serpentine receptors are included in Table 1. Other informative searches used known amino acid sequences of specific serpentine receptors from various species to retrieve expressed sequence tags. For these studies, BLAST 2.0 (Gapped BLAST and Graphical Viewer) with the advanced BLAST option was used. The tblastn program was used to search the dbEST database.

B. In the claims

The amendments to claims 1, 5, 7 and 9 are as follows:

1. (Amended) A method of obtaining a composition substantially enriched in a specific cell type comprising:

contacting a sample of cells with at least one binding agent specific for [an] a serpentine cell surface [marker] receptor indicative of a specific cell type or lineage such that the binding agent binds specifically to a cell or cells [having the marker] expressing the receptor in the sample; and

separating the cell or cells bound by the binding agent from the sample, thereby obtaining a composition substantially enriched in a specific cell type.

2. (Amended) The method of claim 1, further comprising separating from the cell or cells bound by the binding agent [by selecting for] a cell or cells expressing at least one additional marker [associated with a specific cell type].

5. (Amended) The method of claim 4, wherein the antibody is a monoclonal antibody, [or] a polyclonal antibody, or a derivative [thereof] of said antibody.

7. (Amended) The method of claim 1, further comprising analyzing the DNA of the cells to identify a sequence indicative of lineage.

9. (Amended) The method of claim 7, wherein the analyzing is by Southern blot [Blot] analysis.